


SYSTEMATIC REVIEW



Pain management during the withholding and withdrawal of life support in critically ill patients at the end-of-life: a systematic review and meta-analysis

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Abstract

Purpose: To review and summarize the most frequent medications and dosages used during withholding and withdrawal of life-prolonging measures in critically ill patients in the intensive care unit.

Methods: We searched PubMed, EMBASE, the Cochrane Database of Systematic Reviews, and the Virtual Health Library from inception through March 2019. We considered any study evaluating pharmaceutical interventions for pain management during the withholding or withdrawing of life support in adult critically ill patients at the end-of-life. Two independent investigators performed the screening and data extraction. We pooled data on utilization rate of analgesic and sedative drugs and summarized the dosing between the moment prior to withholding or withdrawal of life support and the moment before death.

Results: Thirteen studies met inclusion criteria. Studies were conducted in the United States (38%), Canada (31%), and the Netherlands (31%). Eleven studies were single-cohort and twelve had a Newcastle–Ottawa Scale score of less than 7. The mean age of the patients ranged from 59 to 71 years, 59–100% were mechanically ventilated, and 47–100% of the patients underwent life support withdrawal. The most commonly used opioid and sedative were morphine [utilization rate 60% (95% CI 48–71%)] and midazolam [utilization rate 28% (95% CI 23–32%)], respectively. Doses increased during the end-of-life process (pooled mean increase in the dose of morphine: 2.6 mg/h, 95% CI 1.2–4).

Conclusions: Pain control is centered on opioids and adjunctive benzodiazepines, with dosages exceeding those recommended by guidelines. Despite consistency among guidelines, there is significant heterogeneity among practices in end-of-life care.

Keywords: Pain management, Critically ill, Terminal care, End-of-life

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Introduction

In the USA, 20% of deaths occur in intensive care units (ICUs), and more than 50% of these deaths involve the withholding or withdrawing of life-sustaining interventions [1, 2]. Investigations of the characteristics of this population and the identification of shifts over time in clinical practice are allowing intensivists to better understand and manage patients at the end-of-life [2]. Several guidelines aiming to improve care for these patients have been developed; however, there is significant variation in the care critically ill patients receive at the end-of-life [2, 3].

In 2003, the Robert Wood Johnson Foundation Critical Care End-of-Life peer workgroup and 15 associated physician and nurse teams in North America established seven key elements for quality improvement at the end-of-life, and one of them was symptom management [4]. Pain is one of the most frequently reported symptoms in critically ill patients at the end-of-life, and perception of adequate pain control at the end-of-life reported by next of kin has been observed to range from 47 to 87% [5–8]. This suggests that at least half of these patients die with pain and indicates that pain management is still an area for significant improvement in ICUs and that prioritization of pain management is a marker of medical quality and compassionate care [9].

Pharmacotherapy is considered the cornerstone of palliation, and opioids are the most commonly used medications owing to their capacity to decrease pain, anxiety, and shortness of breath [10]. Concerns, however, arise about the possibility of hastening death due to overmedication. In these cases, the principle of double effect is taken into account, and the foreseen but unintended consequence of shortening the end-of-life process may be accepted as part of the physician's provision of medication intended to relieve suffering [11]. Although ethically validated, the possibility of hastening death deters many clinicians from appropriately increasing doses of analgesics and sedatives at the end-of-life [12]. This concern may be counteracted by implementing multimodal analgesia (the combination of different medications with distinct mechanisms of action), which can minimize the required dosages and associated side effects of opioids [13]. Although using multimodal analgesia at the end-of-life may be beneficial, there is a lack of clarity in how to apply it in patients at the end-of-life, and the literature summarizing pharmacologic interventions for these patients in a systematic way is scarce to nonexistent.

To review and summarize the most frequent medications and dosages used during withholding and withdrawing of life-prolonging measures critically ill patients

Take home message

During the withholding and withdrawing of life support in critically ill patients at the end-of-life, morphine and midazolam were the most common drugs used for pain management.

in the ICU, we conducted a comprehensive systematic review of the literature.

Methods

Protocol and registration

We followed the Cochrane methodology [14]. The protocol was published in the International Prospective Register of Systematic Reviews (PROSPERO), #CRD42018089487. Our report is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15].

Eligibility criteria

We included any original study evaluating pain management during the withholding and withdrawal of life support in adult patients at the end-of-life who were admitted to the ICU. We considered conference abstracts, if they provided sufficient information. We excluded narrative reviews, guidelines, and case reports.

Information sources

We searched electronic databases, including PubMed, EMBASE, Cochrane Database of Systematic Reviews, and the World Health Organization's Biblioteca Virtual en Salud, from database inception through March 2019. No restrictions on language or date were used. Additionally, two reviewers manually searched the bibliography of every relevant citation to identify additional eligible articles otherwise not found.

Search

A professional librarian built a sensitive and specific search strategy based on the terms defined by an anesthesiologist specializing in pain management and two specialists in critical care medicine. The terms used were "pain management" and its synonyms plus specific pharmacologic interventions, combined with the term "end-of-life" and its synonyms, plus "intensive care" and "critical care unit" and their synonyms, with all terms exploded (see Appendix).

Study selection

Two independent investigators (KO and DPD) screened the studies. When disagreements arose on including a

specific article, a third investigator (AL or AD) helped to make the final decision.

Data collection process

Two investigators (AL and AD) independently abstracted information from the included studies using a standard table. Then, the results were compared and a third investigator (JC) resolved disagreements.

Data items

Our primary outcomes were the utilization rates of opioids and analgesics used in critically ill patients in the ICU after withholding or withdrawing life support. Secondary outcomes included doses used in patients at the end-of-life (prior to withholding or withdrawal of life support at 24, 12, and 4 h prior to death and just before death). We extracted information regarding the title, author, country, number of centers involved, objectives, tools implemented, outcomes, and conclusions.

Risk of bias in individual studies

Two independent reviewers assessed the risk of bias in the included studies using the Newcastle–Ottawa Scale for observational studies. The scale evaluates three domains of bias: selection of participants (i.e., representativeness of the cohorts, ascertainment of exposure, and outcome of interest not being present at the start of study), comparability (to accounting for one or more factors (confounders) that predict the outcome of interest), and measurement of outcomes (i.e., methods for outcome assessment, appropriateness of the length of time to assess the outcome, and losses of follow-up do not compromise the validity). This scale consists of a grading system with a maximum score of 9. A score of ≥ 7 points indicates that a study is of high quality [16].

Summary measures

For our primary outcomes, we calculated the utilization rates for each type of medication (either opioids or analgesics). Our denominator was considered as the number of critically ill patients undergoing a specific type of pain management during the withholding and withdrawal of life support at the end-of-life.

Synthesis of results

Data were pooled if sufficient data existed for the primary outcomes (at least two studies reporting utilization rates for the same drug). We used a random-effects model to calculate a combined utilization rate and a 95% confidence interval. We used the Freeman–Tukey arcsine

transformation to stabilize variances and conducted a meta-analysis using inverse variance weights [17, 18]. This methodology has been reported in multiple meta-analysis of binomial data [19–22]. We used a Chi-square test to assess statistical heterogeneity, and we also calculated the percent of the variability in effect estimates that is due to heterogeneity rather than sampling error (I^2 statistic). A Chi-square test with $p < 0.10$ or I -squared statistic $> 50\%$ indicated statistically significant heterogeneity [14]. All analyses were performed using STATA 15 (Stata-Corp LP, College Station, TX, USA). The strength of the evidence resulting from our meta-analysis was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [23]. Findings were classified into high-, moderate-, low-, and very-low-quality evidence according to our confidence in the estimate of effect. Our confidence in the evidence decreased for several reasons, including study limitations, inconsistency of results, indirectness of evidence, imprecision, and reporting bias.

For the secondary outcomes, we reviewed and summarized the evidence using only a narrative synthesis with tabular analysis.

Additional analyses

We planned performing a meta-regression to explore the influence of study characteristics (i.e., eligibility criteria used study design and type of funding) on the utilization rates of opioid and analgesics. Similarly, we planned to perform a funnel plot and a regression asymmetry test to assess small-study bias for the meta-analysis. However, due to the small amount of studies providing utilization rates per drug (< 10 studies) this was not possible.

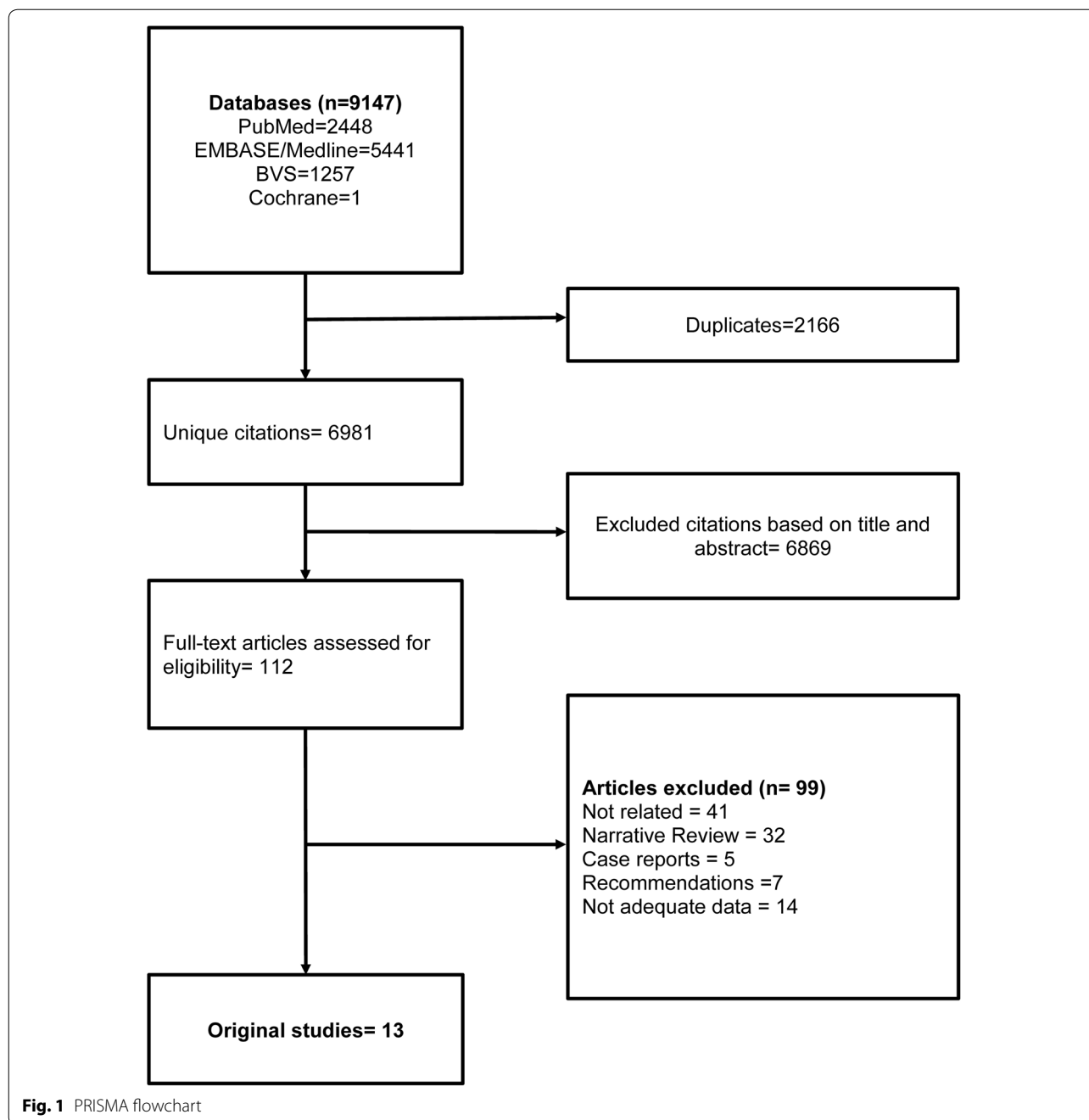
Results

Study selection

We found 6981 unique citations; of these, 112 were retrieved as full text and 13 studies were ultimately included in our analysis [8, 24–35] (Fig. 1; Table 1). For one of the included studies, results regarding pain management or pain control were reported in a post hoc analysis [27, 36].

Study characteristics

Five studies were conducted in the USA [24, 27, 28, 31, 33], four in Canada [8, 29, 30, 32], and four in The Netherlands [25, 26, 34, 35]. All were observational studies (Table 1). Eight studies did not report a funding source, although two received financial support from foundations, one from the National Institutes of Health and one from a critical care trauma center; one did not have financial support. The percentage of male patients in the



studies ranged from 43 to 60%. The mean age ranged from 59 to 71 years. A range of 59–100% of included patients had mechanical ventilation, and life support was actively withdrawn in 47–100% of patients within the included studies.

Risk of bias within studies

Of the 13 studies, 12 had a total Newcastle–Ottawa Scale score <7 (Supplementary Table 1). Eleven studies

evaluated a single cohort of patients without analyzing or comparing with unexposed groups. In eight studies, the population was representative or somewhat representative of the average population. In all studies, the assessment of outcome was confirmed with medical records or linked through a database and the follow-up of the patients was considered adequate.

Table 1 Characteristics of the reviewed articles (13 studies)^a

Lead author, year, country	ICUs (no. of patients)	Design	Inclusion criteria	Outcomes used in this review	Funding
Wilson, 1992, USA [24]	2 (44)	Case series and survey to providers	Critically ill non-brain-dead patients who were expected to die after life support was withheld or withdrawn; 39% had medical; 61% had surgical diagnosis; 84% were not hemodynamically stable; 97% underwent mechanical ventilation at the time of withholding or withdrawal of life support	Use of sedatives/analgesics, time until death	Not reported
Daly, 1996, USA [28]	1 (42)	Retrospective cohort study and survey to nurses	Adult patients who underwent terminal weaning	Use of sedatives/analgesics	Not reported
Keenan, 1997, Canada [29]	3 (419)	Retrospective cohort study	Patients dying in the ICU; mean (\pm standard deviation) age 62.7 ± 16.3 years (60% male); average APACHE II score 25.3 ± 7.8 at admission; major source of patient admissions was general wards; cardiac arrest and sepsis were the most common diagnoses for the subgroup that underwent withdrawal of life support; 50.8% had life support withdrawn, 19.6% had life support withheld, 8.4% were brain dead, and 21.2% died despite treatment	Use of sedatives/analgesics	Richard Ivey Critical Care Trauma Center, Southwestern Ontario Critical Care Research Group
Hall, 2000, Canada [30]	2 (174)	Retrospective cohort study	Patients who died in the ICU; life support withdrawn in 10.3%, sex F/M 69/69, age range 65 ± 16 years, APACHE II score range 25 ± 9 , medical patients 49%; no life support withdrawn in 2.7%, sex F/M 12/24, age range 55 ± 18 years, APACHE II score range 29 ± 9 , medical patients 42%	Use of sedatives/analgesics	Not reported
Hall, 2004, USA [31]	2 (306) ^a	Prospective observational (before and after)	Patients dying in the ICU in whom life support was withheld or withdrawn, including inotropes, mechanical ventilation, dialysis, and others; before withholding or withdrawal: sex F/M 69/69, age range 65 ± 16 years, admission APACHE II score range 25 ± 9 , medical patients 49%, mechanical ventilation at death 59%, time from ICU admission to withholding or withdrawal range 191 ± 260 h, time until death after withholding or withdrawal range 4.3 ± 11.3 h; after withholding or withdrawal: sex F/M 70/98, age range 60 ± 18 years, admission APACHE II score range 23 ± 7 , medical patients 51%, mechanical ventilation at death 60%, time from ICU admission to withholding or withdrawal range 135 ± 205 h, time until death after withholding or withdrawal range 6.1 ± 9.3 h	Use of sedatives/analgesics	Not reported
Rocker, 2004, Canada [8]	6 (206)	Prospective cohort study	ICU patients (length of stay > 48 h) who received mechanical ventilation before life support withdrawal; 75.2% underwent withdrawal of life support; 15.5% had reduced ventilator support; 9.2% died while receiving full mechanical ventilation; mean age (standard deviation) 67.8 years (14.6 years); mean APACHE II score 25.8; sex F/M 89/117; white 93.2%	Use of sedatives/analgesics, pain control perception	Canadian Intensive Care Foundation and Queen Elizabeth II Health Sciences Center Research Foundation

Table 1 (continued)

Lead author, year, country	ICUs (no. of patients)	Design	Inclusion criteria	Outcomes used in this review	Funding
Chan, 2004, Canada [32]	1 (75)	Retrospective cohort study	Patients who had received mechanical ventilation within 1 week before death and had mechanical ventilation discontinued prior to death; mean age 59 years; intracranial hemorrhage 37%; trauma 27%; acute respiratory failure 27%; acute renal failure 20%; sex F/M 53/22	Use of sedatives/analgesics, time until death	Greenwall Foundation and the National Institute of Nursing Research
Mazer, 2011, USA [33]	1 (74)	Prospective cohort study	ICU patients expected to die soon after extubation (terminal withdrawal of mechanical extubation)	Use of sedatives/analgesics, time until death	No financial support
Epker, 2011, The Netherlands [35]	1 (60)	Retrospective cohort study	Patients for whom life-sustaining treatment was withdrawn (mechanical ventilation and vasoactive agents); sex 60% male; mean age 64 years; mean APACHE II score 50; only mechanical withdrawn 61%; mechanical ventilation and vasoactive agents withdrawn 39%	Use of sedatives/analgesics, time until death	Not reported
Epker, 2011, The Netherlands [34]	2 (75)	Prospective cohort study (abstract)	Patients in whom ventilation or vasoactive medication was withdrawn for reason of futility; mean age 69 years; 59% male; common reasons for withdrawal were failure to recover after out-of-hospital cardiac arrest and sepsis with multiple organ failure; mean SOFA score 9.9 on day 1 and 12.4 on the day of withdrawal; mean APACHE II score 31; all patients except one were ventilated; in 81% the ventilation was ceased; 29 patients were extubated	Use of sedatives/analgesics	Not reported
Epker, 2012, THE Netherlands [25]	2 (139)	Prospective cohort study of ICUs at non-academic hospitals (abstract)	Patients who died in the ICU; mean SOFA score 10 at admission and 12 on the day of withdrawal ($p < 0.05$); all but three patients were ventilated; in 93% the ventilation was ceased; 93% received vasoactive medication	Use of sedatives/analgesics, time until death	Not reported
Epker, 2015, THE Netherlands [26]	2 (241)	Prospective cohort study	Adult patients in whom mechanical ventilation and/or vasoactive medication was withdrawn; exclusion criteria included all other causes of death	Use of sedatives/analgesics, time until death	Not reported
Brown, 2016, USA [27]	15 (829)	Unblinded cluster randomized trial (secondary analysis)	Patients with COPD, ILD, or metastatic cancer who died in the ICU; mean age: ILD 72.3 years, COPD 73.6 years, cancer 64 years; female: ILD 39.2%, COPD 40.7%, cancer 47.5%	Pain assessment	The National Institute of Nursing Research of the National Institutes of Health

^a ICU indicates intensive care unit; SOFA, Sequential Organ Failure Assessment; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease

^b Before withdrawal of life support: 138; after withdrawal: 168

Results of the individual studies

Pain management medications used

Eleven studies provided data for our primary outcomes. The utilization rates for each analgesic or adjunctive sedative drug in critically ill patients in the ICU after withholding or withdrawing life support are presented in Figs. 2 and 3, respectively. Eight studies reported the use of opioids without specifying the drug used. The pooled utilization rate of an opioid (unspecified) in critically ill patients in the ICU after withholding or withdrawing life

support was 82% (75–88%). For studies reporting the utilization of specific opioids, morphine was used in 60% of the patients receiving pain management medications (95% CI 48–71%). Other opioids used were sufentanil (58%; 95% CI 52–65%), fentanyl (19%; 95% CI 2–48%), and hydromorphone and meperidine ($\leq 2\%$ of the patients received it).

Similarly, six studies reported the use of an adjunctive sedative without specifying the drug used. The pooled utilization rate of a sedative (unspecified) in critically ill

patients in the ICU after withholding or withdrawing life support was 62% (48–75%). For studies reporting the utilization of specific sedatives, midazolam was used in 28% of the patients receiving pain management medications (95% CI 23–32%). Other adjunctive medications included propofol (24%; 95% CI 12–39%), diazepam (16%; 95% CI 3–36%), and lorazepam (14%, 95% CI 8–21%).

Drug doses for pain management

Five studies compared morphine dosing before the withdrawal of life support with dosing at the moment before death [24, 26, 32, 33, 35]. All five showed a consistent dose increase during the end-of-life process (Table 2). One of these studies reported that in opioid-naïve patients, there was also an increase in mean dose of morphine provided before and after terminal extubation (from 5.2 to 10.6 mg/h, $p=0.001$) [33]. The pooled mean increase in dose was 2.6 mg/h (95% confidence interval 1.2–4) [26, 33]. Three studies also compared midazolam doses [26, 32, 35], two compared doses of fentanyl and lorazepam [32, 35], and two compared doses of propofol [26, 35]; one study compared benzodiazepine dose changes in diazepam equivalents [24].

One study showed a significant increase in the average hourly doses of opioids and benzodiazepines used from the 24 h preceding death to the hour before ventilator withdrawal [32]. Furthermore, the average doses used in the 2 h before death were higher than the average doses used during the previous 22 h ($p<0.001$ for both opioids and benzodiazepines). In another study in patients with withdrawal of life support, morphine doses increased over the 12-h period, particularly in the final 4 h of life [30]. That study also showed a statistically significant difference in the dosages of morphine and lorazepam between patients who died undergoing withdrawal of life support and those who died without limitations of life support ($p<0.007$ and $p<0.006$, respectively). Doses of other medications did not statistically differ between these two groups [30]. Rocker et al. found that dosages used did not differ among three time periods before death (4 h, 4–8 h, and 12 h), and the cumulative dose in the last 4 h did not differ between modes of withdrawal of life support (e.g., extubation, T-piece or trach hood, weaning mechanical ventilation, full ventilator support) [8].

Discussion

With this systematic review of the literature, we were able to identify published pharmacologic practices of pain management during the withholding or withdrawal of life support in the ICU. We found that opioids were the most common analgesic used (up to 88%), with morphine the most common, followed by fentanyl. Adjunctive

benzodiazepines were used in 45–82% of patients; midazolam was the most common sedative used in most of the studies. Regarding medication dosages, we found that the mean dosing of analgesics and sedatives both before and after withholding or withdrawal of life support was consistent with the ranges used for withdrawal of life support in previous studies [24, 29].

Doses reported in many of the reviewed documents were higher than recommended dosages in guidelines for critically ill patients at the end-of-life [3]. This could be explained by the development of opioid tolerance in a considerable proportion of critically ill patients who are at the end-of-life, as evidenced by one study in which more than half of patients were already receiving opioids prior to withholding or withdrawing of life support [33]. We identified a progressive increase in drug dosing preceding the withdrawal of life support, which may reflect adjustments needed to alleviate discomfort during the end-of-life, despite unease about shortening the process [11]. This concern has been questioned by some recent studies showing prolongation of or no effect on time until death with the use of these medications [24, 26, 32, 33, 37], and a Cochrane systematic review found no statistically significant difference in the duration of the end-of-life process between sedated and non-sedated patients in the hospice palliative care setting [38].

Although there is homogeneity among end-of-life critical care guidelines, our systematic review showed a wide variation in practice and medication use, which could be attributed to the individualization of care recommended by guidelines, underuse of standardized protocols, or lack of guideline specificity in the recommendations [3, 39–41]. Of note, among the more recent studies included in this review, we observed that the frequency of use was lower for morphine and higher for fentanyl compared to the earlier studies included. This observation may be attributable to fentanyl's easier titration, faster onset of action, and more favorable side effects profile [42]. Sedatives were employed during end-of-life care in the majority of included studies, suggesting the appropriate association of sedation to analgesia, a key pillar of palliative care medicine [43, 44].

Early cooperation with palliative care services could improve the final care these patients receive; additionally, the implementation of multimodal analgesia may also be beneficial at the end-of-life [2, 3, 45–47]. While the latter is favorable for patients in other circumstances, such as perioperative and trauma cases, we found a lack of evidence investigating this therapeutic approach during the withholding and withdrawal of life support [48, 49]. The use of non-opioid medications can reduce opioid requirements and their side effects, such as pruritus, nausea, and constipation, which are undesirable during

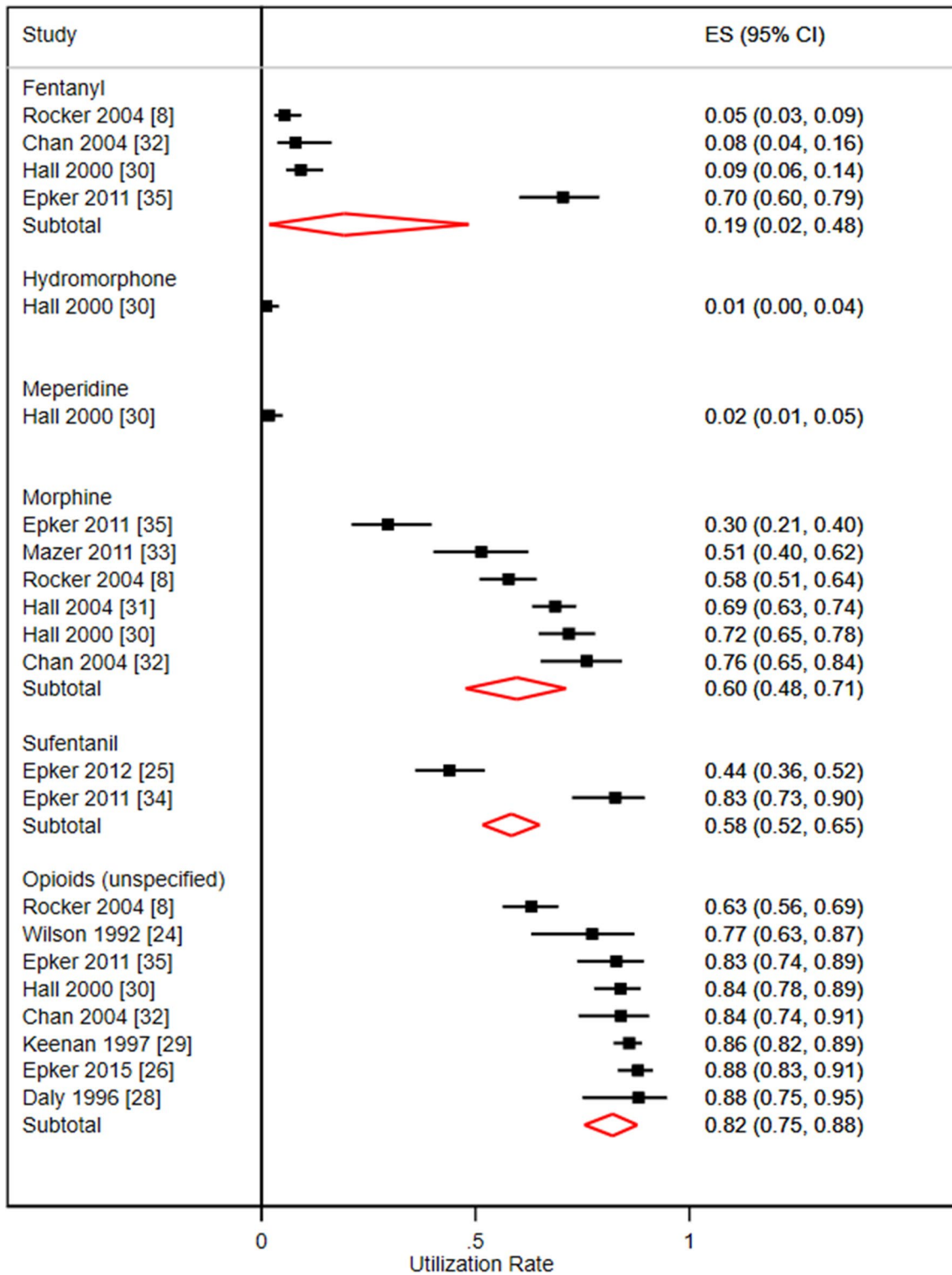


Fig. 2 Frequency of analgesic drugs used during end-of-life care in the intensive care unit (horizontal bars indicate 95% confidence intervals; black squares [ES; proportion used], effect estimate referred as utilization rate; size of the squares, weight of the effect; red diamonds, pooled percentage used for each type of drug)

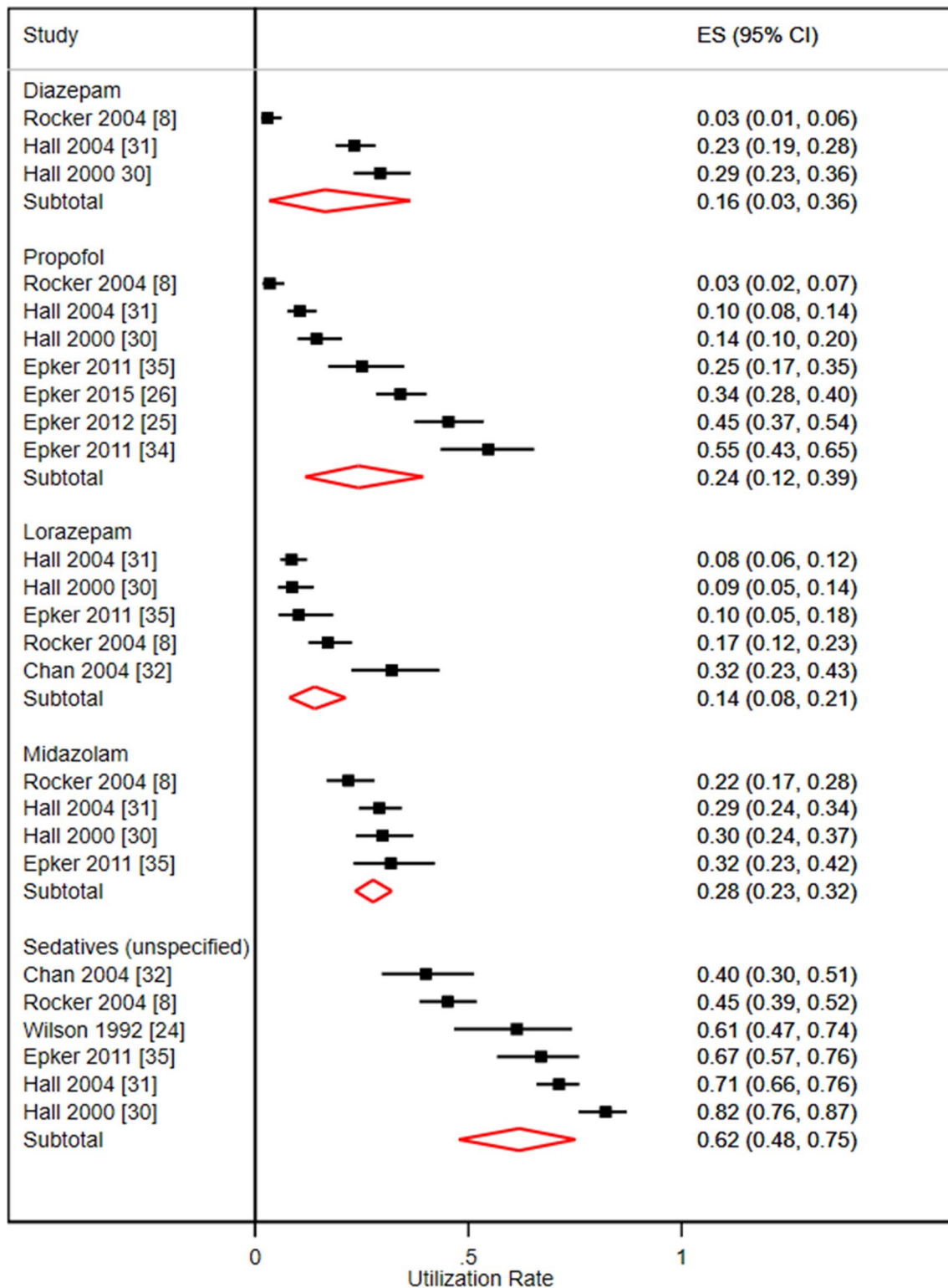


Fig. 3 Frequency of sedative drugs used during end-of-life care in the intensive care unit (horizontal bars indicate 95% confidence intervals; black squares [ES; proportion used], effect estimate referred as utilization rate; size of the squares, weight of the effect; red diamonds, pooled percentage used for each type of drug)

Table 2 Differences in opioid and sedative dosing between the moment prior to withholding or withdrawal of life support (WWLS) and the moment before death

Study	Time periods compared	No	Mean \pm SD (mg/h)	Range (mg/h)	Mean change of dose (mg/h)
Morphine					
Wilson 1992 ^a [24]	Before WWLS	34	3.3 \pm 1.2	–	7.9 ($p < 0.001$)
	During WWLS	34	11.2 \pm 2.0	–	
Chan 2004 [32]	1 h before WWLS	63	15.6	1–106	2.0
	2 h before death	63	17.6	1–143	
Epker 2011 [35]	4 h before death	15	5.5 (4–10) ^b	1–30	0.5
	1 h before death	15	6 (5–10) ^b	1–10	
Mazer 2011 [33]	Before WWLS	24	10.2 \pm 5.6	2.5–20	5.3 ($p < 0.022$)
	Before death	24	15 \pm 12.3	2.0–53.3	
Epker 2015 [26]	Before WWLS	185	11.7 \pm 8.38	–	2.3 ($p < 0.002$)
	Before death	213	14.04 \pm 8.34	–	
Midazolam					
Chan 2004 [32]	1 h before WWLS	30	8.2	1.6–18.6	– 0.8
	2 h before death	30	7.4	1–15	
Epker 2011 [35]	4 h before death	19	8 (5–14.5) ^b	2–25	0.5
	1 h before death	19	8.5 (5–15.5) ^b	2–25	
Epker 2015 [26]	Before WWLS	111	12.2 \pm 7.5	–	1.6 ($p < 0.002$)
	Before death	129	13.8 \pm 9.8	–	
Propofol					
Epker 2011 [35]	4 h before death	15	134 (41–236) ^b	4–415	– 0.019
	1 h before death	15	160 (41–270) ^b	4–758	
Epker 2015 [26]	Before WWLS	78	186 \pm 96.9	–	27.7 ($p < 0.002$)
	Before death	83	213.7 \pm 113.2	–	
Fentanyl^c					
Chan 2004 [32]	1 h before WWLS	63	322	25–1222	– 0.019
	2 h before death	63	303	13–1277	
Epker 2011 [35]	4 h before death	35	100 (60–169) ^b	20–500	0
	1 h before death	35	100 (86–223) ^b	20–500	
Lorazepam					
Chan 2004 [32]	1 h before WWLS	30	8.6	0.1–35	1.7
	2 h before death	30	10.3	0.5–36	
Epker 2011 [35]	4 h before death	6	1.3 (0.7–5.5) ^b	0.3–14	0.4
	1 h before death	6	1.7 (0.7–5.9) ^b	0.3–14	
Diazepam^d					
Wilson 1992 ^a [24]	Before WWLS	27	2.2 \pm 0.7	–	7.6 ($p < 0.03$)
	Before death	27	9.8 \pm 3.2	–	

^a Data are for maximum doses during WWLS in this study, rather than those immediately before death

^b Median mg/hour (interquartile range)

^c Fentanyl doses are reported in mcg/hour

^d Reported doses are for all benzodiazepines expressed in diazepam equivalents.

the end-of-life process. Several case reports have shown positive effects of medications such as ketamine, dexmedetomidine, and regional anesthesia at the end-of-life in the ICU [50–52], but the lack of clinical studies and practice parameters limits the applicability of this approach in

patients at the end-of-life, and thus, further investigation should be prioritized.

Our review has some limitations. First, citations may have been disregarded by our search strategy, mainly due to the variability of terms used in the literature to

describe the end-of-life processes in the ICU. However, to overcome this limitation, all terms were reviewed and complemented by two anesthesiologists and a research librarian who performed reference and hand searches before the final database search was started. A second limitation was the heterogeneity of the reviewed studies and their relatively small sample sizes; all of them were non-controlled, observational studies. The lack of randomized controlled trials may be explained by the difficulty in measuring outcomes of pain management in this population. In addition, due to the small number of studies reporting data on the utilization rates of opioids or analgesics, we were not able to explore the influence of potential confounders (e.g., eligibility criteria used, study design, type of funding, etc.) on the pooled percent of patients using each drug. Therefore, our results should be interpreted with caution. Further research studies are needed and likely may have an important impact on our confidence in the reported pooled utilization rates of the drugs.

In summary, the current systematic review outlines the frequency and dosing of medications used for pain management during the withholding and withdrawal of life support in the ICU. We found that pain control centered on opioid and adjunctive benzodiazepine use with dosages exceeding those recommended by guidelines and that while current guidelines are homogenous, there is significant heterogeneity among practices in this setting.

Electronic supplementary material

The online version of this article (<https://doi.org/10.1007/s00134-020-06139-7>) contains supplementary material, which is available to authorized users.

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Authors' contributions

AL, AD-C, and JLN conceived the study. CIF developed the search strategy and performed the literature search. AL, AD-C, JAC, CoF, KO, and DPD did the study selection and data extraction for the systematic review. MAL-O performed

the formal analysis. AL, AD-C, and JLN wrote the first draft of the manuscript. All authors contributed to the interpretation of data and critical revision of the manuscript and approved the final manuscript. All authors confirm the accuracy and integrity of the work.

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Compliance with ethical standards

Conflicts of interest

The authors declare no conflict of interest directly applicable to this research.

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References

1. Angus DC, Barnato AE, Linde-Zwirble WT et al (2004) Use of intensive care at the end of life in the United States: an epidemiologic study. *Crit Care Med* 32:638–643
2. Sprung CL, Ricou B, Hartog CS et al (2019) Changes in end-of-life practices in European intensive care units from 1999 to 2016. *JAMA* 322:1692–1704. <https://doi.org/10.1001/jama.2019.14608>
3. Durán-Crane A, Laserna A, López-Olivo MA et al (2019) Clinical practice guidelines and consensus statements about pain management in critically ill end-of-life patients. *Crit Care Med* 47:1619–1626. <https://doi.org/10.1097/CCM.0000000000003975>
4. Clarke EB, Curtis JR, Luce JM et al (2003) Quality indicators for end-of-life care in the intensive care unit. *Crit Care Med* 31:2255–2262. <https://doi.org/10.1097/01.CCM.0000084849.96385.85>
5. Mularski RA, Heine CE, Osborne ML et al (2005) Quality of dying in the ICU: ratings by family members. *Chest* 128:280–287. <https://doi.org/10.1378/chest.128.1.280>
6. Gerritsen RT, Jensen HI, Koopmans M et al (2018) Quality of dying and death in the ICU. The euroQ2 project. *J Crit Care* 44:376–382. <https://doi.org/10.1016/j.jcrc.2017.12.015>
7. Phelan D, Weld J, Curran MR et al (2009) A study to evaluate the end-of-life care provided by a critical care service. *Intensive Care Med* 35:S263
8. Rocker GM, Heyland DK, Cook DJ et al (2004) Most critically ill patients are perceived to die in comfort during withdrawal of life support: a Canadian multicentre study. *Can J Anaesth* 51:623–630. <https://doi.org/10.1007/BF03018407>
9. Curtis JR, Rubenfeld GD (2001) *Managing death in the intensive care unit. The Transition from Cure to Comfort*. Oxford University Press, New York
10. Barr J, Fraser GL, Puntillo K et al (2013) Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the Intensive Care Unit: executive summary. *Am J Heal Syst Pharm* 70:53–58
11. Quill TE, Dresser R, Brock DW (1997) The rule of double effect—a critique of its role in end-of-life decision making. *N Engl J Med* 337:1768–1771. <https://doi.org/10.1056/NEJM199712113372413>
12. Hawryluck LA, Harvey WRC, Lemieux-Charles L, Singer PA (2002) Consensus guidelines on analgesia and sedation in dying intensive care unit patients. *BMC Med Ethics* 3:E3
13. St Marie B (2013) Pain management in patients receiving palliative care. *Oncol Nurse Advis* 20:e1–e6
14. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (2019) *Cochrane handbook for systematic reviews of interventions*, 2nd edn. Wiley, Chichester
15. Liberati A, Altman DG, Tetzlaff J et al (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate

- health care interventions: explanation and elaboration. *J Clin Epidemiol* 62:e1–e34. <https://doi.org/10.1016/j.jclinepi.2009.06.006>
16. Stang A (2010) Critical evaluation of the Newcastle–Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 25:603–605. <https://doi.org/10.1007/s10654-010-9491-z>
 17. Nyaga VN, Arbyn M, Aerts M (2014) Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Public Health* 72:39. <https://doi.org/10.1186/2049-3258-72-39>
 18. Trikalinos TA, Trow P, Schmid CH (2013) Simulation-based comparison of methods for meta-analysis of proportions and rates. *Methods Res Rep*
 19. Akowuah PK, Kobia-Acquah E (2020) Childhood obesity and overweight in Ghana: a systematic review and meta-analysis. *J Nutr Metab* 2020:1–11. <https://doi.org/10.1155/2020/1907416>
 20. Wang Q, Xu K, Xie W et al (2020) Seroprevalence of H7N9 infection among humans: a systematic review and meta-analysis. *Influenza Other Respir Viruses*. <https://doi.org/10.1111/irv.12736>
 21. Fabbri A, Parker L, Colombo C et al (2020) Industry funding of patient and health consumer organisations: systematic review with meta-analysis. *BMJ*. <https://doi.org/10.1136/bmj.l6925>
 22. Lin T-C, Yoshida K, Tedeschi SK et al (2018) Risk of hepatitis B virus reactivation in patients with inflammatory arthritis receiving disease-modifying antirheumatic drugs: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken)* 70:724–731. <https://doi.org/10.1002/acr.23346>
 23. Schünemann H, Brożek J, Guyatt G, Oxman A (2013) GRADE handbook for grading quality of evidence and strength of recommendations. In: *Grade Work. Gr.* www.guideline/development.org/handbook. Accessed 13 May 2020
 24. Wilson WC, Smedira NG, Fink C et al (1992) Ordering and administration of sedatives and analgesics during the withholding and withdrawal of life support from critically ill patients. *JAMA* 267:949–953
 25. Epker JL, Kompanje EJO (2012) Opioids and sedatives do not seem to contribute to time till death after withdrawal of life-sustaining therapy in Dutch critically ill ICU patients. *Intensive Care Med* 38:S242–S243. <https://doi.org/10.1007/s00134-012-2683-0>
 26. Epker JL, Bakker J, Lingsma HF, Kompanje EJO (2015) An observational study on a protocol for withdrawal of life-sustaining measures on two non-academic intensive care units in the Netherlands: few signs of distress, no suffering? *J Pain Symptom Manage* 50:676–684. <https://doi.org/10.1016/j.jpainsymman.2015.05.017>
 27. Brown CE, Engelberg RA, Nielsen EL, Curtis JR (2016) Palliative care for patients dying in the intensive care unit with chronic lung disease compared with metastatic cancer. *Ann Am Thorac Soc* 13:684–689. <https://doi.org/10.1513/AnnalsATS.201510-667OC>
 28. Daly BJ, Thomas D, Dyer MA (1996) Procedures used in withdrawal of mechanical ventilation. *Am J Crit Care* 5:331–338
 29. Keenan SP, Busche KD, Chen LM et al (1997) A retrospective review of a large cohort of patients undergoing the process of withholding or withdrawal of life support. *Crit Care Med* 25:1324–1331
 30. Hall RI, Rocker GM (2000) End-of-life care in the ICU: treatments provided when life support was or was not withdrawn. *Chest* 118:1424–1430
 31. Hall RI, Rocker GM, Murray D (2004) Simple changes can improve conduct of end-of-life care in the intensive care unit. *Can J Anaesth* 51:631–636. <https://doi.org/10.1007/BF03018408>
 32. Chan JD, Treece PD, Engelberg RA et al (2004) Narcotic and benzodiazepine use after withdrawal of life support: association with time to death? *Chest* 126:286–293
 33. Mazer MA, Alligood CM, Wu Q (2011) The infusion of opioids during terminal withdrawal of mechanical ventilation in the medical intensive care unit. *J Pain Symptom Manage* 42:44–51. <https://doi.org/10.1016/j.jpainsymman.2010.10.256>
 34. Epker JL, Bakker J, Kompanje EJO (2011) Withdrawing mechanical ventilation and vaso-active medication in Dutch non-academic ICUs: a prospective study focused on sedative and opioid use, comfort of the patient, severity of illness and time till death. *Intensive Care Med* 37:569
 35. Epker JL, Bakker J, Kompanje EJO (2011) The use of opioids and sedatives and time until death after withdrawing mechanical ventilation and vaso-active drugs in a Dutch intensive care unit. *Anesth Analg* 112:628–634. <https://doi.org/10.1213/ANE.0b013e31820ad4d9>
 36. Curtis JR, Treece PD, Nielsen EL et al (2008) Integrating palliative and critical care: evaluation of a quality-improvement intervention. *Am J Respir Crit Care Med* 178:269–275. <https://doi.org/10.1164/rccm.200802-272OC>
 37. Edwards MJ (2005) Opioids and benzodiazepines appear paradoxically to delay inevitable death after ventilator withdrawal. *J Palliat Care* 21:299–302
 38. Beller EM, van Driel ML, McGregor L et al (2015) Palliative pharmacological sedation for terminally ill adults. *Cochrane Database Syst Rev* 1:CD010206. <https://doi.org/10.1002/14651858.CD010206.pub2>
 39. Patrick DL, Engelberg RA, Curtis JR (2001) Evaluating the quality of dying and death. *J Pain Symptom Manage* 22:717–726
 40. Curtis JR, Patrick DL, Engelberg RA et al (2002) A measure of the quality of dying and death: initial validation using after-death interviews with family members. *J Pain Symptom Manage* 24:17–31. [https://doi.org/10.1016/S0885-3924\(02\)00419-0](https://doi.org/10.1016/S0885-3924(02)00419-0)
 41. Lanken PN, Terry PB, DeLisser HM et al (2008) An official American Thoracic Society clinical policy statement: palliative care for patients with respiratory diseases and critical illnesses. *Am J Respir Crit Care Med* 177:912–927. <https://doi.org/10.1164/rccm.200605-587ST>
 42. Panahi Y, Dehcheshmeh HS, Mojtahedzadeh M et al (2018) Analgesic and sedative agents used in the intensive care unit: a review. *J Cell Biochem* 119:8684–8693. <https://doi.org/10.1002/jcb.27141>
 43. Cherny NI, Radbruch L (2009) European Association for Palliative Care (EAPC) recommended framework for the use of sedation in palliative care. *Palliat Med* 23:581–593. <https://doi.org/10.1177/0269216309107024>
 44. Robert R, Le Gouge A, Kentish-Barnes N et al (2020) Sedation practice and discomfort during withdrawal of mechanical ventilation in critically ill patients at end-of-life: a post-hoc analysis of a multicenter study. *Intensive Care Med*. <https://doi.org/10.1007/s00134-020-05930-w>
 45. Mathews KS, Nelson JE (2017) Palliative care in the ICU of 2050: past is prologue. *Intensive Care Med*. <https://doi.org/10.1007/s00134-017-4828-7>
 46. Puntillo K, Nelson JE, Weissman D et al (2014) Palliative care in the ICU: relief of pain, dyspnea, and thirst—a report from the IPAL-ICU Advisory Board. *Intensive Care Med* 40:235–248. <https://doi.org/10.1007/s00134-013-3153-z>
 47. Ely EW, Azoulay E, Sprung CL (2019) Eight things we would never do regarding end-of-life care in the ICU. *Intensive Care Med* 45:1116–1118. <https://doi.org/10.1007/s00134-019-05562-9>
 48. Buvanendran A, Kroin JS (2009) Multimodal analgesia for controlling acute postoperative pain. *Curr Opin Anaesthesiol* 22:588–593. <https://doi.org/10.1097/ACO.0b013e328330373a>
 49. Hamrick KL, Beyer CA, Lee JA et al (2019) Multimodal analgesia and opioid use in critically ill trauma patients. *J Am Coll Surg* 228:769–775.e1. <https://doi.org/10.1016/j.jamcollsurg.2019.01.020>
 50. Noreika DM, Coyne P (2015) Discontinuance of life-sustaining treatment utilizing ketamine for symptom management. *J Pain Palliat Care Pharmacother* 29:37–40. <https://doi.org/10.3109/15360288.2014.1003686>
 51. O'Hara C, Tamburro RF, Ceneviva GD (2015) Dexmedetomidine for sedation during withdrawal of support. *Palliat Care* 9:15–18. <https://doi.org/10.4137/PCRT.S27954>
 52. Schulz-Stübner S, Boezaart A, Hata JS (2005) Regional analgesia in the critically ill. *Crit Care Med* 33:1400–1407. <https://doi.org/10.1097/01.ccm.0000165843.39713.ae>